

Evaluation of Human Arterial Endothelial Function using a Single Blood Pressure Cuff

Cardiovascular disease (CVD) is a major health challenge in both the developed and developing world. According to the World Health Organization, CVD is responsible for 29.2% of global deaths, 80% of these in low and middle-income countries. By 2010, CVD is predicted to be the leading cause of death in the Third World. The incidence and socio-economic burden of CVD can be reduced through medication (principally statins), smoking cessation, as well as lifestyle and dietary modification. **The ultimate goal of this invention is to provide individuals frequent feedback regarding their cardiovascular (CV) status. In this way, the effects of preventive measures in an individual can be monitored, even on a day-to-day basis. This will serve to identify those interventions that are most effective for a particular person and reinforce positive behavioral modifications and compliance with drug interventions.**

Dysfunction of the arterial endothelium (cells that line the arteries) is widely believed to be a necessary condition for the development of atherosclerotic disease. Perhaps for this reason, endothelial dysfunction (ED) is a powerful early predictor of incipient disease that often begins in childhood. In patients with known atherosclerosis, ED predicts future CV events, such as heart attack and stroke. It has been shown to maintain independent predictive value even when diagnostic measures such as cholesterol and C-reactive protein levels are known. **The endothelium acts as armor, actively protecting the artery from plaque build-up and preventing the blood carried by the artery from clotting. Arguably, plaque accumulation on the arterial wall is not possible when the endothelium is functioning properly. This invention can determine the strength of this armor in a convenient and cost-effective way.**

Currently, non-invasive measurements of endothelial function (EF) in arteries require expensive and bulky equipment such as an ultrasonic imaging machines. While, simpler, more compact commercial systems are currently available for EF measurement, these cost approximately \$25,000 and assess microvascular endothelial function only. Microvascular measurements enjoy limited clinical acceptance, especially because atherosclerosis is primarily a disease of arteries rather than the microcirculation. Also, while EF in the brachial artery of the arm has been shown to be highly correlated to EF in the coronary arteries, there is a paucity of data on the correlation of coronary and microvascular EF. **This invention enables endothelial function measurements to be performed in the arteries of the arm using a simple blood pressure (BP) cuff. Consequently, the envisaged cost of the device will be similar to that of BP measurement devices for home use (less than \$50 to the consumer).**

Consider a scenario in which an individual checks their endothelial function (EF) once a day. According to hundreds of published studies, their EF will be impaired if this person has been smoking that day or has indulged in a large fatty meal. An individual who is complying poorly with cholesterol-lowering medication will see their EF decrease towards levels typical of the premedication period. Conversely, healthy diet and exercise will often be immediately reflected in a more favorable EF reading. No other test provides such near-immediate feedback.

Currently, CVD risk is assessed through questionnaire analysis of risk factors and blood tests. These measures are not sensitive to day-to-day and week-to-week influences on the CV system. It is unfortunate that the development of *in vitro* diagnostic tests is almost exclusive focus of research in this field, with physical measures such as that proposed being neglected. There is considerable confounding interplay between *in vitro* measures such as LDL cholesterol and individual genetic factors. The purpose of this proposal is to make a clear and direct measurement of the fundamental integrity of the endothelium. Endothelial cells (ECs) are our primary defense against atherosclerosis. Functioning ECs produce nitric oxide (NO) that prevents platelet aggregation (the cause of blood clots) and macrophage adhesion (the cause of fatty plaque build up on the arterial wall). The proposed device measures the ability of endothelial cells to produce NO, regardless of an individual's phenotype or genotype. In contrast to *in vitro* analyses, the proposed method will identify when the endothelium is in a state such that arteries are vulnerable to injury (and the progression of atherosclerosis), thus providing feedback to the individual and primary care clinician.

Commercialization of this invention is likely to succeed because: (1) It offers a practical means to address the World's largest medical problem via a preventive approach. The decrease in CVD

morbidity and mortality in the West is to a significant extent due to improvements in surgical interventions, a strategy that is too expensive for Third World. **A tool that provides an individual with feedback is as essential for preventing and managing CVD as a scale and tape measure are for weight-loss programs.** (2) The instrument is low-cost and the measurement procedure requires no technical skill on the part of the operator. (3) The method is based on the sound physical and physiological principles we now outline.

EF can be measured non-invasively by comparing the cross section of an artery before and after stimulus of the endothelium. Such stimulus can be provided by increasing the blood flow in the vessel. Faster flow increases shear stress on the ECs, stimulating the cells to produce NO. Diffusion of NO into the surrounding vascular smooth muscle leads to muscle relaxation, dilating the vessel. An accepted way of producing increased flow is to occlude the vessel with a cuff for a period of 3-5 minutes. When the cuff is released, reactive hyperemia ensues, during which blood flow increases \approx 5-10 times over baseline. When EF is intact, the vessel diameter increases after cuff release, with maximum dilation occurring approximately one minute after release. Currently, the vessel diameter change is measured using ultrasound imaging. This is a very technically-challenging procedure, and inter-observer and inter-laboratory variability is very high as a consequence. It requires that the subject remain motionless for several minutes. In the present technique, **we measure area change rather than diameter change.** We do this using the same cuff used to induce RH, in a completely automated procedure.